performed 5-9 days after baseline) and week 2 (defined as the latest assessment performed 12-16 days after baseline). There were no statistically significant differences in these pairwise comparisons for the number of patients presenting an increase of laboratory parameters.

Changes in liver function, clotting factors and platelets after 1 and 2 weeks of treatment (see above for how week 1 and week 2 were defined) were presented in detail and are summarized here:

Groups I vs. III: N (%) of Patients With Increase From Baseline in Liver Function and Platelets After 1-2 Weeks of Treatment (note: the denominator for each group represents the total number of patients in that group who had the specific laboratory parameter measured; under the n (%), is stated if the baseline value for that specific parameter was normal or abnormal. Since no patient had an increase in clotting factors after 1-2 weeks of treatment, they are not included in the table below):

Laboratory Parameter	Group I		Group III	
	Week 1 N (%)	Week 2 N (%)	Week 1 N (%)	Week 2 N (%)
ALT (SGPT)	1/15 (7%) base. abnl.	0/7 (0%)	2/14 (14%) base. abnl. in 2	2/12 (17%) base. abnl. in 2
AST (SGOT)	2/15 (13%) base. nl. in 1 & abnl. in 1	2/7 (29%) base. nl. in 1 & abnl. in 1	3/15 (20%) base. nl. in 1 & abnl. in 2	2/12 (17%) base. nl. in 1 & abnl. in 1
Alkaline Phosphatase	1/13 (8%) base. nl.	0/7 (0%)	1/11 (9%) base. abnl.	2/12 (17%) base. nl. in 1 & abnl. in 1
Total bilirubin	2/15 (13%) base. nl. in 1 & abnl. in 1	1/7 (14%) base. nl.	1/16 (6%) base. nl.	1/12 (8%) base. nl.
Biliary acids	1/5 (20%) base. abnl.	½ (50%) base. abnl.	0/3 (0%)	0/2 (0%)
Platelets	1/14 (7%) base. nl.	1/7 (14%) base. nl.	3/16 (19%) base. nl. in 3	5/12 (42%) base. nl. in 5

A similar analysis was done comparing groups I/II to III/IV:

Laboratory Parameter	Group I/II		Group III/IV	
	Week 1 N (%)	Week 2 N (%)	Week 1 N (%)	Week 2 N (%)
ALT (SGPT)	4/30 (13%) Base. nl. in 3 & abnl. in 1	0/16 (0%)	7/28 (25%) base. nl. in 5 & abnl. in 2	4/22 (18%) base. nl. in 2 & abnl. in 2
AST (SGOT)	4/31 (13%) Base. nl. in 3 & abnl. in 1	2/16 (13%) base. nl. in 1 & abnl. in 1	6/29 (21%) base. nl. in 4 & abnl. in 2	4/22 (18%) base. nl. in 3 & abnl. in 1
Alkaline Phosphatase	2/28 (7%) Base. nl. in 2	1/16 (6%) base. nl.	2/25 (8%) base. nl. in 1 & abnl. in 1	2/21 (10%) base. nl. in 1 & abnl. in 1
Total bilirubin	2/31 (6%) Base. nl. in 1 & abnl. in 1	1/16 (6%) base. nl.	1/30 (3%) base. nl	1/22 (5%) base. nl.

Biliary acids	3/9 (33%) Base. nl. in 1	¼ (25%) base. abnl.	¼ (25%) base. nl.	0/3 (0%)
Platelets	6/30 (20%) Base. nl. in all	2/15 (13%) base. nl. in all	8/31 (26%) base. nl. in all	11/23 (48%) base. nl. in all

Conclusions:

Liver function showed no significant differences between patients with liver disease who were treated with Cernevit vs. those treated with Soluvit/Vitalipid for 1-2 weeks. However, a higher percentage of patients treated with Cernevit for 1-2 weeks experienced elevations in bile acid levels compared to those who received Soluvit/Vitalipid. This was postulated to be related to the mixed micelles in Cernevit. It was previously demonstrated by other investigators (Darragh, Ballinger and Farthing), that glycocholic acid is quickly cleared by the liver after IV administration in healthy subjects. However, in patients with chronic liver disease, the hepatic extraction of bile acids is reduced, resulting in a rise in serum concentrations. The investigators of this study concluded that there was no significant difference in adverse drug reactions in patients with and without liver disease as well as compared to control therapy with Soluvit/Vitalipid. Therefore, Cernevit can be safely administered to patients with advanced liver disease.

There was 1 study of 15-55 days duration (i.e. maximum: ~ 8 weeks duration) (safety study):

Study ID: R6: Title:Safety of Cernevit in Patients Treated for More Than 15 Days

Investigator: Dr. Colin Study site: France Date of study: 1990-93

The study was a retrospective analysis on a subgroup of 22 patients who had been enrolled in a prospective, open, multicenter, randomized trial whose objective was to compare 2 lipid emulsions: 20% CSW 6-3 to 20% Intralipid, to each other. The purpose of this retrospective analysis was to evaluate the hepatic safety of Cernevit.

22 patients (14 M and 8 F, mean age of 29 yrs. and range of 17-66 yrs.) who required TPN for at least 15 days, received Cernevit. 19 of these patients had Crohn's disease, 1 short bowel syndrome, 1 occlusion of colectomy (neoplasia) and 1 peritonitis (neoplasia) with malnutrition. Patients with severe hepatic dysfunction and patients in whom the enteral intake represented >10% of the daily caloric intake were excluded (note: 3 of the 22 patients in this study received enteral supplementation but intake was <10% of total nutritional intake). Lipids were infused during 4-5 hrs. Then, a solution composed of glucose, amino acids, micronutrients and Cernevit (1 vial/day) was infused over 10-12 hrs. This regimen continued daily for a mean of 23 days (range: 15-55 days).

Results:

In the following parameters, the mean change from baseline to endpoint was statistically significant ($p < 0.05$):

Hematological: mean wbc decreased from 10.2×10^3 at baseline to 8.35×10^3 at the end of the study ($p= 0.05$); mean platelets decreased from baseline of 492,000 to 365, 000 at study end ($p< 0.001$) and mean PT time increased from 79.2% at baseline to 88.8% at endpoint ($p= 0.04$). The investigator regarded these changes as reflective of the relatively good control of the patients' underlying inflammatory disease.

Hepatic: mean serum bile acids increased from 5.81 umol/l at baseline to 9.24 umol/L at study end (normal: <6 umol/L), $p= 0.01$. Biliary acids increased during the study in 7/22 patients (32%). In 1 of these 7 patients, the increase was transient, returning to normal levels at study end. There was no statistically significant change in mean transaminases, alkaline phosphatase, gamma GT, 5' nucleotidase, total or conjugated bilirubin, gamma globulin or lipase. However, ALT (SGPT) showed a trend towards an increase (mean baseline ALT was 22.6 IU/L which increased to 25.9 IU/L at study end). In 1 patient, there was a significant increase (twice the initial value) in ALT.

Echography to assess hepatobiliary complications occurring during the study, was performed in 17 patients. In 8/17 (47%), abnormalities were noted during the study:

Sludge in 5 (3 on study day 15; 1 on day 30 and 1 on day 35; in 1 of these 5 patients, Sludge was associated with cholestasis),

Hepatomegaly in 3 patients (one of whom also developed sludge, hepatomegaly was noted on day 15 in 2 patients and day 35 in 1)

Lithiasis in 1 patient on day 15.

The sludge and lithiasis were considered to be related to TPN. Hepatomegaly is multifactorial. None of the events were regarded as related to Cernevit.

Conclusions:

Cernevit was well tolerated over an average treatment period of 3 weeks. Although bile acid levels significantly increased on Cernevit, it was not accompanied by a significant increase in transaminases, gamma GT or other elevations in liver function. Furthermore, it was not related to biliary sludge. Therefore, the investigator regarded this change in bile acid levels to be of no clinical significance. The hepatobiliary echography changes were expected in patients undergoing parenteral nutrition.

There was 1 study of 3 months duration and it is an efficacy and safety study:

Study ID: R4: Title: "Safety of Cernevit in Patients Treated During 3 Months" Investigator: Dr. Joyeux Study site: France Date of study:1990-1993

This was a prospective, open, non-comparative 3 month trial in 20 patients, 9 M and 11 F, ages 32-70 yrs. old, requiring home parenteral nutrition. The diagnoses in these 20 patients was: 9 had short bowel (2 also with Crohn's, 9 with radiation enteritis, 3 with GI fistulae, 1 with severe celiac disease and 1 with GI amyloid). The purpose of the study was to determine if Cernevit 1 vial/day, added to TPN, could normalize or maintain in the normal range, over a 3 month period, plasma concentrations of the lipid-soluble vitamins (A, D and E). In addition, the study aimed to evaluate the hepatic safety of Cernevit. Cernevit served as the sole source of vitamins. (Note: patients were excluded from this trial if they had received either oral or parenteral vitamin supplementation one month before entry).

Patients were monitored for clinical signs of vitamin deficiency as well as plasma concentrations of vitamins D, E and A at baseline and sequentially during the study (days 14, 30, 45, 60, 75 and 90). Safety monitoring included hematology, calcium, phosphorous, magnesium, AST/ALT, bilirubin, albumin, retinol binding protein, triglycerides and total cholesterol.

Results:

4 patients had clinical symptoms of vitamin deficiency at baseline: all had smooth tongue and in 2, it was associated with desquamation of the skin. Deficiencies of vitamins B and C were suspected and, in 2 patients, also of vitamin A. However, the B and C vitamins were not measured in this study. Vitamin A levels were low at baseline in both patients in whom the deficiency was suspected. These signs were no longer present by study day 60 in any patient. (Note: vitamin A levels normalized during the study in both patients in whom it was deficient at entry).

The mean ± SD plasma concentration of the lipid soluble vitamins at baseline and end of study (3 months) follows:

Vitamin	Normal value	Baseline Mean + SD (Range)	3 Months Mean + SD (Range)	p value
Vit D(1,25-OH)	19-67 pg/ml	15.7 ± 11.2 (4.0-36.0)	21.6 ± 11.8 (7.0-47.0)	0.002
Vit D (25-OH)	7-27 pg/ml	11.3 ± 7.2 (5.9-27)	14.5 ± 5.9 (7.0-27)	0.003
Vit A	1-2.6 umol/l	1.7 ± 0.7 (0.11-2.9)	2.4 ± 0.7 (1.4-3.6)	0.00001
Vit E	12-38.4 umol/l	10.5 ± 5.7 (2.4-25.3)	13.1 ± 3.9 (6.8-23.8)	0.005

The initially low mean concentrations of 1,25-OH vitamins D and E, normalized under vitamin replacement. The mean concentrations of vitamins A and 25-OH vitamin D remained in the normal range.

Comments regarding vitamin levels in individual patients:

Vitamin D (25-OH) was normal in all patients at the end of the trial, including 7 patients with low levels at baseline.

Vitamin D (1,25-OH) was normal at study end in 11/20 patients, 3 of whom had low levels at baseline. Therefore, vitamin D (1,25-OH) remained low in 9/20 patients (45%). (Note: the 1,25-OH vitamin D levels in these 9 patients were: 7-14 pg/ml in 8 patients and 17 pg/ml in one patient).

Vitamin A levels normalized in the 3 patients who had low levels at baseline.

Vitamin A levels were high in 3/20 patients (15%) at baseline and were high in 8/20 (40%) at study end. (Note: vitamin A levels in these 8 patients were: between 2.7-2.9 umol/l in 3 patients and between 3.0-3.6 umol/l in 5 patients).

Although vitamin E levels improved in every one of the 14 patients who had a low level at baseline, in only 2, did the level normalize. In 1 patient with a normal baseline vitamin E, the levels decreased below normal on days 45 and 90. Therefore, vitamin E levels were low at the end of the study in 13/20 patients (65%). (Note, however, in 6 of these 13 patients, the vitamin E level was only slightly below normal: 11.8-11.9 umol/l. However, vitamin E levels were between 6.8-11.2 umol/l in the other 7 patients). In summary, vitamin E and 1,25-OH D remained low in the majority of the patients.

There were no signs of clinical intolerance (fever, tremor, pruritus or jaundice). There were no clinically meaningful changes in mean values for hematology parameters, calcium, phosphorous, magnesium, bilirubin, alkaline phosphatase or lipids. Serum albumin and retinol binding protein became normal in all patients and mean liver transaminases significantly decreased, probably reflecting improved nutritional status. However, in 1 patient (5%), normal baseline transaminase levels became abnormal during the study: AST increased to 1.1 x normal and ALT, to 2.6 x normal at study end.

There was 1 safety study of 15-405 days duration (however, safety data was presented and analyzed only for 6 weeks of exposure to Cernevit):

Study ID: R7: Title: Cernevit: Long-Term Tolerance in Adults
Investigator: Dr. Colin Study site: France Date of study: 1988-1991

This study was a retrospective comparison of patients who received Cernevit (1 vial/day) administered in TPN (glucose, amino acid and micronutrient portion of TPN) and infused over 10-11 hrs. (group I) to patients in whom TPN was supplemented with different vitamin formulations (Hydrosol Polyvitamine administered in TPN and vitamin B12 and Folic Acid, IM or IV)- group II. The investigator states the latter was administered in recommended dosages. (Note: the Cernevit administered here differs from the currently marketed preparation in that the former contains vitamin D: 220 IU, B12: 0.006 mg and biotin 0.069 mg while in the latter, the respective quantities are: 200 IU, 0.0055 mg and 0.06 mg).

Safety monitoring included serum transaminases, alkaline phosphatase, gamma GT, total bilirubin and PT measured at baseline and after 4 weeks and 6 weeks of TPN.

Results:

Although 27 patients were enrolled in group I and 20 in group II, only 20 and 13 patients, respectively were included in the study analysis because duration of TPN administration was either <4 weeks or varying lipid emulsions comprising the TPN were used. Group I comprised 12 F and 8 M, mean age of 45.2 yrs; group II comprised 10 F and 3 M, mean age of 36.7 yrs. Mean duration of time on TPN was 119 days (17 weeks) for group I and 40 days (~6 weeks) for group II. The duration of treatment with Cernevit in TPN ranged from 27-405 days and, in those not receiving Cernevit: 25-56 days. The diagnoses in group I patients (n= 20) were: 10 with Crohn's disease, 5 with short bowel syndrome, 2 with GI fistulae, 1 with peritonitis, 1 with complications of Lyell's disease and 1 with "multiple interventions to the bowel". The diagnoses in group II patients were: 6 with Crohn's disease, 1 with acute pancreatitis, 1 with "occlusion", 1 with complications of peritonitis, 2 with caustic ingestion and 2 patients with other GI disturbances.

No signs of either local or systemic intolerance to Cernevit were noted during the study.

Group I (n= 18 patients with 4 week data and 15 with 6 week data) vs. Group II (n= 13 patients with 4 week data and 6 with 6 week data):

Except for mean alkaline phosphatase which was higher in group I, liver function tests were comparable between the 2 groups at baseline.

Comparison between groups for the mean change in liver function tests and PT from baseline to week 4: the only significant difference between groups was for AST (SGOT) where the difference from baseline to week 4 was: – 1 IU/l for group I and +15 IU/l for group II ($p< 0.02$).

Comparison between groups for the mean change in liver function tests and PT from baseline to week 6: there were no statistically significant differences between the groups.

Note: in only 1 patient in group I, was there a significant increase in any of these liver function tests during the 6 weeks of Cernevit administration. Alkaline phosphatase

markedly increased at week 6. This patient's condition was stated to have markedly deteriorated due to a recurrence of a pelvic neoplasm.

In patients with Crohn's disease, 10 in group I and 6 in group II, ALT was elevated at the end of the study in 1/10 patients in group I and 2/6 patients in group II. The group I patient had a baseline ALT (SGPT) of 94 IU/l, at 4 weeks of 19 IU/l and at endpoint of 81 IU/l. This same patient had severe Crohn's disease which required treatment with steroids and immunosuppressants. The ALT elevation regressed when these medications were reduced/discontinued. In both group II patients, ALT was normal at baseline but biliary sludge and an abdominal abscess developed in these patients during the course of the study.

General Safety and Adverse Events:

Over 13 million units have been sold since 1988 and there have been only 6 reports of adverse events, 2 of which have been urticaria. One case of anaphylaxis was reported in the literature with a mixed micelle preparation of vitamin K (see section on Safety of Mixed Micelles, report by Havel on page 7 of this review).

These 6 reports are:

2 cases of urticaria following Cernevit administration (one in a 7 yr. old F and one in a 52 yr. old F). The route and rate of Cernevit administration are unknown,

1 case of anaphylaxis occurred in a 31 yr. old F with Crohn's disease. The patient was hospitalized with an acute septic episode. She received antibiotics, immunosuppressants and steroids, as well as TPN and Cernevit. On the 12th hospital day, she received an IV injection of Cernevit over 3-4 minutes. Approximately 2 minutes later, she went into cardiac arrest and could not be resusitated. This event was recorded as having a doubtful relationship to Cernevit,

1 case of hypercalacemic coma following administration of 2 ampules Protovit MM (route and rate unknown) in a patient (age and sex unknown) with a history of chronic renal failure,

1 patient with several febrile episodes on days when Cernevit (1 vial 3x/week) was administered in parenteral nutrition. The patient, age 56 yrs., was receiving PN for short bowel syndrome. She was hospitalized and blood and catheter cultures were negative. Endotoxin testing of the same lot of Cernevit was negative. On re-introduction of the same lot, no further febrile episodes occurred,

1 patient with injection site pain following IM administration of 1 ampule of Protovit MM.

Therapeutic Drug Interactions:

Drug interactions may relate to both the vitamins and the mixed micelles. For example, folic acid and pyridoxine have been reported to influence the concentration of several drugs such as phenytoin and phenobarbital. Pyridoxine can reduce the effect of levodopa. Dexpanthenol (B5) has been associated with a rare cases of allergic reaction during concomitant use with antibiotics, opiates and barbiturates. However, the sponsor's rationale for not including this in the labeling is that these combinations are common, and, therefore, the occurrence of this type of reaction must be extremely rare.

Glycocholic acid binds to albumin and lecithin to lipoproteins. 2 studies of mixed micelles examined the interactions of glycocholate and effects of binding bilirubin or exogenous substances to albumin in the serum of healthy human subjects. The first study is described and summarized in the section on Safety of Mixed Micelles, report by Guentert et al, page 5 of this review. The results of this study will be reiterated briefly here. Either a mixed micelle solution (117 mmol/L glycocholic acid and 96 mmol/L lecithin) or a glycocholate solution (117 mmol/L) was combined with neonatal serum obtained from cord blood and adult serum obtained from 6 healthy volunteers. The study examined the influence of glycocholate or mixed micelle solution on the binding of bilirubin to albumin as measured by the displacement of monoacetyldiaminodiphenylsulfone (MADDS), a deputy ligand for bilirubin (competes with bilirubin for binding to albumin). The objective of this study was to determine the reserve albumin for binding of bilirubin in human serum in either the presence or absence of mixed micelles. The addition of 351 umol/L glycocholate to 1 ml adult serum, resulted in a decrease in reserve albumin of 31% $\pm$ 11% or 32% $\pm$ 10% when free glycocholate or mixed micelles, respectively was used. Results in neonatal serum were similar: 35% $\pm$ 6% free glycocholate, 31% $\pm$ 4.7%, mixed micelles. It did not make a significant

difference whether glycocholate was added alone or as mixed micelles (95% confidence limits for the difference: -2% to +6%).

In a second study, Guentert et al (Br J Clin. Pharmac. 1987, 23:569-577), studied the efffect of mixed micelles (glycocholic acid 88.5 mg/ml and lecithin 169.3 mg/ml) on the binding of drugs known to have a high affinity for albumin (diazepam, warfarin, ketoprofen, furosemide, probenicid) and/or other serum proteins: alpha 1-acid glycoprotein (prazosin, propranolol, quinidine or diosopyramide) or to transcortin (prednisolone). Human serum was added to one of two different drug concentrations corresponding to the upper and lower end of the therapeutic range for that drug, then combined with various concentrations of the mixed micelle preparation. At concentrations corresponding to "therapeutic" concentrations of mixed micelles (0.177 mg glycocholate/ml serum), the mixed micelles had minimal to no effect on the protein binding of drugs known to bind exclusively to albumin or transcortin. However, when the higher concentration of the mixed micelle solution was used (0.885 mg glycocholate/ml serum, corresponding to at least 5 times that expected in adults after injecting a 6 ml dose by IV bolus), a significant increase (up to 45%) occurred in the free fraction of drugs with a high affinity for albumin. Furthermore, a 50-80% increase occurred in the free fraction of drugs known to bind to alpha 1-acid glycoprotein, even at "therapeutic" doses of mixed micelles. At 5x the "therapeutic" dose of mixed micelles, the unbound fractions of these drugs increased 2- to 3-fold.

Drug Compatibility:

Folic acid has been reported to be unstable in the presence of calcium gluconate. Thiamine, riboflavin, pyridoxine, niacin and ascorbic acid have been reported to decrease the antibiotic activity of erythromycin, kanamycin, streptomycin, oxycycline and lincomycin. Bleomycin is reportedly inactivated in vitro by vitamin C and riboflavin. Cernevit-12 should not be admixed directly into a lipid emulsion; however, it may be added to a lipid containing parenteral nutrition admixture and administration should be completed within 24 hrs..

Smith et al (reference 31: J of Parenteral and Enteral Nutrition 12 (4):394-402, 1988), studied the effects of phototherapy, bisulfite and pH on vitamin stability in TPN admixtures. The following summarizes these findings:

1. Exposure of TPN admixtures to phototherapy, results in losses of vitamins A, C and riboflavin.
2. Admixtures containing Intralipid reduce losses of vitamin A and riboflavin
3. Addition of 2-3 mEq/L bisulfites, minimizes losses of vitamin A but concentrations > 3 mEq/L results in massive losses of vitamin A even in the presence of Intralipid- 25% loss of vitamin A after 24 hrs. and 50% loss after 48 hrs. High bisulfite concentration ($\geq$ 3 mEq/L), results in massive losses of thiamine.
4. As pH increases, vitamin C losses increase; the addition of $\geq$ 3 mEq/L bisulfites, helps to minimize the losses of vitamin C. Increasing pH appears to protect against thiamine loss, particularly when combined with low bisulfite concentration.
5. Smith et al conclude that since commercially available amino acid solutions all contain bisulfite and varying pH, the above data indicate that IV vitamins should be added to TPN admixtures immediately prior to administration and administration should be completed within 24 hrs.

Dahl et al (reference 48: J of Enteral and Parenteral Nutrition 1194, 18: 234-239) studied the stability of vitamins following direct admixture to a lipid emulsion, Intralipid 10%. Fat-soluble vitamins A, D and E, as well as thiamine, pyridoxine and folic acid, were found stable for 24 hrs. at room temperature. Vitamin K, riboflavin and C losses were 6-17%, 10-20% and 9-52%, respectively. Dahl states that young children received ~70% of the initial amount of ascorbic acid.

Evaluation and Regulatory Action:

3 issues will be summarized and discussed:

1. The safety of the mixed micelle excipient in humans (note: glycocholic acid, a bile acid, binds to albumin; and lecithin, to lipoproteins)

2. The adequacy of the preparation to meet the needs of patients ≥ 11 yrs.
3. The adequacy of the preparation to meet vitamin requirements in pediatric patients from 1-11 yrs. of age

Regarding the safety of mixed micelles (MM) administered alone to humans:

13 studies examined the safety of mixed micelles. 9 of these were single dose studies only. One of the trials, (Manesme et al), studied both single and multiple doses of mixed micelles (up to 3 months in children with biliary atresia and chronic cholestasis) and the remaining three studies were each 4-6 days in duration.

Single Dose MM Studies:

In the single dose studies, either a vitamin K or valium mixed micelle preparation was administered. The objective of the majority of these studies was to compare local and systemic tolerability and PK parameters between the standard drug (valium or vitamin K alone) and the corresponding drug containing mixed micelles (Valium MM or Vitamin K MM). Some studies compared the 2 Valium preparations for time to onset of sedation. The single dose study in newborns was to determine the efficacy of Vitamin K MM to prevent hemorrhagic disease of the newborn. The route of administration included po, IM or IV injection.

7 of these single dose studies were conducted in adults. In 5 of these studies in adults, the dose given ranged from 1.26- 4x the amount of glycocholic acid contained in a daily dose of Cernevit and was 3-9x for lecithin. In one other study in adults, the amount of MM administered was less than in Cernevit (40% for glycocholic acid and 67% for lecithin). In the remaining adult study, Valium MM was administered "until the eyelid reflex was suppressed". Local and systemic tolerance was comparable between the preparation without MM and that with MM. In one of these adult studies (Charkiolaki et al), a circumscribed chest rash occurred in 2/50 patients (4%) who received Diazemuls (diazepam in soya bean oil and water) vs. 2% (1/50) who received Valium MM. Vital signs, when measured, were comparable between the preparations. Administration by IV bolus of 4x the amount of glycocholic acid contained in a daily dose of Cernevit and 9 x for lecithin, displaced monoacetyldiaminodiphenylsulfone, MADDS (a deputy ligand for bilirubin), from albumin very quickly with peak displacement occurring within 3-10 minutes after injection. The maximum mean decrease was 68% in males and 45% in females and the effect was maintained for 20 minutes. Also following MM injection, serum nonesterified fatty acids rose markedly particularly in males (mean rise: 473%, with a mean rise in females of 143%). On the other hand, esterified fatty acids decreased (mean : 18% for females and 21% for males).

3 of these single dose MM safety studies were conducted in pediatric patients, ages: newborns to 13 years. Compared to the MM content in a daily dose of Cernevit recommended for those ≥ 11 yrs., the dose of glycocholic acid in these studies was 12%, 40% and 126% and, for lecithin, 20%, 67% and 300%. The only notable findings were in the newborn vitamin K study (oral vitamin K without MM: 7 newborns, oral vitamin K MM: 15 newborns and IM vitamin K MM: 8 newborns). An isolated elevation in SGOT was noted 24 hrs. after dosing in 25/30 newborns (the breakdown by treatment group was not specified). Liver enymes were normal at 1 month of age in all newborns. Also, 1 infant who received mixed micelles IM, required a blood transfusion at 1 month of age for anemia.

Multiple Dose MM Studies:

There were 4 multiple dose MM studies. 3 of these 4 studies were conducted in adults and were of 4-6 days duration. The study in children was of 3 months duration.

At ~1.2 x the amount of glycocholic acid in a daily dose of Cernevit and 2 x that for lecithin, administered by IV injection for 4 consecutive days, there was no difference in hematology and biochemistry profiles between vitamin K without MM (n= 15 adults) compared to that with MM (n= 15), nor were any local reactions observed. However, an anaphylactoid reaction occurred in 1/15 patients (7%) who received the MM. 3 minutes after IV injection of Vitamin K MM, the patient became flushed, lost consciousness and became hypotensive. He recovered within 10 minutes of receiving fluids and antihistamines.

IV infusion over 1 hour of 5x the amount of glycocholic acid contained in a daily dose of Cernevit, resulted in a significant increase in serum glycocholic acid compared to placebo. Although there was a significant difference between MM and placebo for hemoglobin and rbc counts, the difference was not clinically relevant. 1 patient receiving MM reported heartburn which was considered only remotely related to the test drug.